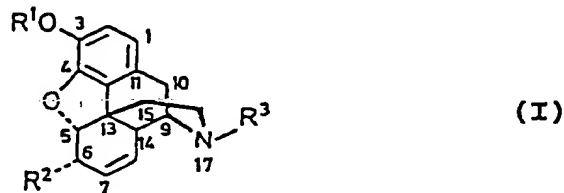


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ACIDIC ADDITION SALTS OF MORPHINE ALKALOIDS AND THE USE  
THEREOF

The invention relates to substances consisting essentially of the acid addition salt of a morphine alkaloid and an organic acid, said morphine alkaloid having the following formula I:



where  $R^1$  is selected from the group consisting of H,  $C_1$ - to  $C_6$ -alkyl residues, preferably methyl, ethyl, propyl, isopropyl,  $C(O)CH_3$ ;  $R^2$  selected from the group consisting of H, OH,  $OC(O)CH_3$ ,  $=O$ ,  $=CH_2$ ;  $R^3$  selected from the group consisting of  $-CH_3$ , cyclopropyl, cyclobutyl and allyl; and where the bond at C7/C8 may be saturated or a nitroxyl group may be present at  $N_{17}$ .

Morphine alkaloids, especially morphine, belong to the group of strong analgesics; their therapeutic use lies, inter alia, in the field of treatment of intense and extremely intense conditions of pain occurring, for example, in many cases of carcinosis in the final stage, or following accidents.

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A1 The heretofore existing possibilities of administration (oral, parenteral) employing these substances are dissatisfactory. There is a danger of acid-catalyzed chemical changes taking place in the stomach. In addition, these administration forms result in high variations in the plasma

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 27 level, which are observed, in particular, in the case of parenteral application (injection). Due to the plasma concentrations obtained either falling short of or exceeding the therapeutically desired plasma concentrations, habit-forming effects occur.

From US-A 4,626,539 pharmaceutical compositions are known containing an opioid substance, e.g. morphine, or pharmaceutically acceptable salts thereof. Pharmaceutically acceptable salts described in this patent document are acetates, napsylates, tosylates, succinates, hydrochlorides, palmitates, stearates, oleates, parmoates, laurates, valerates, hydrobromides, sulfates, methane sulfonates, tartrates, citrates and maleates.

From US-A 5,374,645 there are known compositions for the transdermal administration of ionic pharmaceutically active agents, whereby morphine or its pharmaceutically acceptable salts is among the substances mentioned in this context. Salts mentioned in addition to the above morphine salts are oxalates, pyruvates, cinnamates, acetates, trifluoroacetates as well as salicylates and some other substances.

US-A 4,879,297 describes pharmaceutical compositions containing opioids or the pharmaceutically acceptable salts thereof, describing as salts in particular those of certain fatty acids such as palmitates, stearates, oleates and parmoates.

Furthermore, in US-A 4,908,389 active substance-containing compositions for topical application are described containing the active substances in the form of acid addition salts such as hydrochlorides, hydrobromides, orthophosphates, benzoates, maleates, tartrates, succinates, citrates, salicylates, sulfates or acetate.

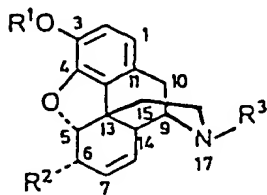
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The dermal or topical application of one of the above-stipulated acid-addition salts of morphine alkaloids has the disadvantage of very poor skin permeability of the salts mentioned. In the case of the known compositions it is attempted to compensate this drawback by adding so-called enhancers to the administration forms.

Even though this method sometimes leads to the desired success, it would be preferable, from a pharmaceutical or therapeutic point of view as well under the aspect of legal approval, if morphine alkaloid salts were available that per se had a higher permeability through the skin, so that no additional substance would be required or only a small amount thereof. The reason for this being, in particular, that the use of the above-mentioned enhancers, even if applied on the skin, leads to disadvantageous effects such as skin irritations or undesired pharmacodynamic side effects due to excessive toxicity.

Thus, it is the object of the present invention to provide acid addition salts of morphine alkaloids of the above-mentioned formula I which have improved properties as compared to the known salts. In particular, their permeability through the skin is to be increased.

This object is solved by providing a substance consisting substantially of the acid addition salt of a morphine alkaloid and an organic acid, said morphine alkaloid having the following formula I:



(I)

where  $R^1$  is selected from the group consisting of H,  $C_1$ - to  $C_6$ -alkyl residues, preferably methyl, ethyl-, propyl, i-propyl,  $C(O)CH_3$ ;  $R^2$  selected from the group consisting of the monad residues H, OH,  $OC(O)CH_3$ , whereby in this case the fourth valence of the (6)-C atom is occupied by H, or the dyad residues  $=O$ ,  $=CH_2$ ;  $R^3$  is selected from the group consisting of  $-CH_3$ , cyclopropyl, cyclobutyl and allyl; and where

- the bond at C7/C8 may be saturated, or a nitroxyl group may be present at  $N_{17}$

and the organic acid is selected from:

- monoesters of  $C_3$ - to  $C_{16}$ -dicarboxylic acids with monohydric  $C_1$ - to  $C_4$ -alcohols, especially methanol,
- $C_2$ - to  $C_{16}$ -sulfonic acids,
- substituted benzoic acids, selected from the group of halogen-, hydroxy-, alkyl-, hydroxyalkyl-, alkoxyalkyl- and/or alkoxy-substituted benzoic acid, as well as of the aminosubstituted benzoic acids, which may optionally be alkylated at the N atom.
- substituted or non-substituted 5-ring or 6-ring heterocycles comprising at least one N or S atom and having a carboxyl group function, especially a carboxy, carboxymethyl, carboxyethyl or the - optionally branched - carboxypropyl or carboxybutyl groups as substituents,

- saturated or unsaturated, optionally substituted, oxo-carboxylic acids having 5 to 10 C atoms,
- phenyl-substituted or phenoxy-substituted saturated C<sub>2</sub>- to C<sub>4</sub>-carboxylic acids.
- aliphatic, aromatic or heterocyclic C<sub>2</sub>- to C<sub>12</sub>-amino acids, wherein an amino group is substituted with an - optionally substituted - C<sub>2</sub>- to C<sub>6</sub>-alkanoyl group or an - optionally substituted - benzoyl group.

Preferred embodiments are the subject-matter of the sub-claims.

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A1 The substance according to the invention substantially consists of an acid-addition salt of a morphine alkaloid of the aforementioned formula I and a further organic acid. The term "substantially consisting of" signifies that impurities are contained only to an extent which is common. The substance respectively the composition according to the present invention can be prepared and purified employing methods commonly used in preparative organic chemistry, so that the purified substance can also be provided in p.A. or p.p.A. purity. The acid is, in particular, pharmaceutically acceptable. It, too, can be produced by means common methods if it is not yet available on the market.

In the case of the morphine alkaloid of the above-mentioned formula I, R<sup>1</sup> is selected from the group consisting of H, C<sub>1</sub>- to C<sub>6</sub>-alkyl residues and C(O)CH<sub>3</sub>. The C<sub>1</sub>- to C<sub>6</sub>-alkyl residues preferably are methyl, ethyl, propyl or i-propyl residues. The R<sup>2</sup> residue is a monad residue from the group of H, OH, OC(O)CH<sub>3</sub>, the fourth valence at the (6)-C atom in this case being occupied by H. As an alternative, R<sup>2</sup> may

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also be one of the dyad residues  $=O$  or  $=CH_2$ .  $R^3$  is selected from the group consisting of  $-CH_3$ , cyclopropyl, cyclobutyl and allyl. Furthermore, the double bond between C7/C8 may be saturated. Apart therefrom, a nitroxyl group may be present at N 17. In the above-numerated organic residues, C(O) refers to a carbonyl function.

The acid component of the acid-addition salt according to the present invention is selected from monoesters of  $C_3$ - to  $C_{16}$ -dicarboxylic acids with monohydric  $C_1$ - to  $C_4$ -alcohols, from  $C_2$ - to  $C_{16}$ -sulfonic acids, from substituted benzoic acids selected from the group of halogen, hydroxy, alkyl, hydroxyalkyl, alkoxyalkyl-substituted and/or amino-substituted benzoic acids, the latter optionally being alkylated at the N atom, from substituted or non-substituted, saturated or unsaturated 5-ring or 6-ring heterocycles having at least one N atom or S atom and having one of the already mentioned carboxyl group functions as substituents, a carboxyl group being especially preferred as substituent, from saturated or unsaturated - optionally substituted - oxocarboxylic acids having 5 to 10 C atoms, or from phenyl-substituted or phenoxy-substituted saturated  $C_2$ - to  $C_4$ -carboxylic acids, especially acetic acid. Naturally,  $C_3$ - to  $C_{16}$ -dicarboxylic acids here refer to carboxylic acids having a total carbon number of 5 to 18 C atoms.

The alkyl, hydroxyalkyl or alkoxyalkyl-substituted benzoic acids are, above all, those, wherein the alkyl residue or even alkoxy residue at the benzoic acid nucleus has 1 to 12 C atoms. These alkyl or alkoxy residues may also be branched. Examples therefor are i-propyl, 2-methylpropyl, t-butyl residues, 2-methylbutyl residues or the corresponding alkoxy residues. The benzoic acid nuclei may also be polysubstituted; as a matter of course, they may also be

substituted with various of the alkyl or alkoxy residues mentioned.

What has been said above regarding the alkyl or alkoxy residues at the benzoic acid nucleus of the alkyl-substituted or alkoxy-substituted benzoic acids also applies - with reference to the alkyl or alkoxy part of the alkoxyalkyl residue in respect of the number of carbon atoms or the branching - in the case of benzoic acids substituted with alkoxyalkyl residues.

Also possible and preferred as alkoxy substituents in preferred alkoxyalkyl-substituted benzoic acids are  $C_1$ - to  $C_6$ -alkoxy groups, especially methyloxy, ethyloxy or propyloxy groups. These alkoxy groups are etherified with  $C_1$ - to  $C_4$ -hydroxyalkyl, especially with hydroxymethyl, hydroxyethyl or hydroxypropyl groups.

The aminosubstituted benzoic acids may optionally also be alkylated at the amino group - in particular with  $C_1$ - to  $C_4$ -alkyl residues.

Preferred substituted benzoic acids are halogen,  $C_1$ - to  $C_6$ -alkyl, hydroxy- ( $C_1$ - to  $C_6$ )-alkyl, amino-substituted or hydroxy-substituted benzoic acids. The amino-substituted benzoic acids may in turn be substituted at the amino group - as explained above. In the case of aminobenzoic acid, the amino group is, in preferred embodiments, either non-substituted or monosubstituted or disubstituted with  $C_1$ - to  $C_4$ -alkyl groups. Especially preferred alkyl-substituted benzoic acids are monosubstituted or polysubstituted  $C_1$ - to  $C_4$ -alkyl-substituted benzoic acids, preferably  $C_1$ - to  $C_4$ -trialkyl-substituted benzoic acids, whereby the alkyl residues may also vary.

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Examples for preferred hydroxyalkyl-substituted benzoic acids are hydroxymethylated, hydroxyethylated, hydroxypropylated or hydroxybutylated benzoic acids.

Among the above-stipulated hydroxy-substituted benzoic acids, the p- or m-hydroxy-substituted benzoic acids are especially preferred.

Most preferred among the substituted benzoic acids for the acid component of the acid-addition salts of morphine alkaloids of the above-mentioned Formula I according to the present invention are p-hydroxybenzoic acid, p-aminobenzoic acid or trimethylbenzoic acid, especially 2,4,6-trimethylbenzoic acid.

The substituted or non-substituted 5-ring or 6-ring heterocycles used according to the invention as acid components for morphine alkaloid acid addition salts are cyclic 5-ring or 6-ring systems comprising at least one nitrogen or S atom, such as, in particular, pyridine, piperidine, pyrimidine or analogous pyrrole or thiophene ring systems. These ring systems additionally carry a carboxyl group at one ring atom. Naturally, the heterocyclic ring system may also be saturated, as is already evident from the piperidine ring system.

The 6-ring heterocycles are, preferably, substituted or non-substituted pyridinecarboxylic acid, especially nicotinic acid. Among the preferred 5-ring systems having at least one S-atom there is lipoic acid.

As mentioned above, the morphine alkaloid acid addition salts may, with respect to the acid component, also consist of C<sub>2</sub>- to C<sub>16</sub>-sulfonic acids. Of these sulfonic acids,



C<sub>4</sub>- to C<sub>8</sub>-sulfonic acids, especially hexanesulfonic acid, are particularly preferred.

The monoesters of C<sub>3</sub>- to C<sub>16</sub>-dicarboxylic acids with monohydric C<sub>1</sub>- to C<sub>4</sub>-alcohols, especially methanol, used in the case of the morphine alkaloid acid addition salts according to the present invention are preferably monoesters of C<sub>5</sub>- to C<sub>10</sub>-dicarboxylic acids with the above-mentioned alcohols.

In this context, substances especially preferred as acids are suberic acid, azelaic acid or sebacic acid. Among the aforementioned monoesters of dicarboxylic acids, monomethylsebacate is most preferred.

If, in accordance with the invention, a saturated or unsaturated, e.g. olefinically unsaturated, and optionally substituted, oxocarboxylic acid having 5 to 10 C atoms is used as acid component of the morphine-alkaloid acid addition salt, preferably this is - optionally olefinically unsaturated - 2-, 4-, 5- or 9-oxocarboxylic acid. Among these oxocarboxylic acids, 5-oxopyrrolidine-2-carboxylic acids (pyroglutamic acid), levulinic acid or oxo-dec-2-ene acid are the most advantageous.

If as an acid component for the morphine alkaloid acid addition salts according to the invention a phenyl-substituted or phenoxy-substituted C<sub>2</sub>- to C<sub>4</sub>-carboxylic acid is used, this is preferably a phenyl-substituted or phenoxy-substituted acetic, propionic or butyric acid.

The aliphatic, aromatic or heterocyclic C<sub>2</sub>- to C<sub>12</sub>-amino acids used according to the invention are preferably monoaminomonocarboxylic acids, wherein the amino group is sub-

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stituted with a C<sub>2</sub>- to C<sub>6</sub>-alkanoyl group, which may be mono- or polysubstituted with hydroxy, C<sub>1</sub>- to C<sub>4</sub>-alkoxy- or C<sub>1</sub>- to C<sub>4</sub>-hydroxyalkyl, or wherein the amino group is substituted with the benzoyl residue, which may be mono- or polysubstituted with C<sub>1</sub>- to C<sub>4</sub>-alkyl, C<sub>1</sub>- to C<sub>4</sub>-alkoxy, C<sub>1</sub>- to C<sub>4</sub>-hydroxyalkyl, halogen, amino or hydroxy.

The aromatic amino acids may be, for example, phenyl amino acids, preferably phenylalanine and tyrosine; the heterocyclic amino acids are preferably proline, hydroxyproline and tryptophan. Especially preferred are, however, aliphatic C<sub>2</sub>- to C<sub>6</sub>-monoaminomonocarboxylic acids, wherein the amino group is substituted, as indicated above; it is, however, especially preferred if the amino group is substituted with the acetyl group or benzoyl group.

The alkaloid component of the morphine alkaloid acid addition salts according to the present invention are preferably the morphine alkaloids morphine, codeine, heroin, ethylmorphine, levorphanol or hydromorphone.

Generally, of the above-mentioned acid addition salts according to the invention those are especially preferred whose molecular mass (MW) is below 800, preferably below 600, and most advantageously between 400 and 600.

According to the invention there are also provided mixtures of the above-mentioned substances, whereby either the same morphine alkaloid is reacted with various acid components, or the same acid component is combined with various morphine alkaloids. Of course, such a composition may also contain a combination of the two aforementioned variants. In a preferred embodiment, the composition is a solution or suspension of the acid addition salts according to the invention in glycerol, ethyl ne glycol, oleic acid, dimeth-

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ylisosorbide and/or dimethylsulfoxide, wher by such solution or suspension may also contain further components, such as penetration enhancers.

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AJ Especially preferred penetration enhancers are polyoxethyl-ene sorbitane fatty acids, such as Tween 20, or polyoxyethylene alcohols, such as, for example, polymerisation products of up to 10 molecules ethylene oxide, each with one molecule octanol, decanol or dodecanol, or mixtures of these polimerization products.

The morphine alkaloid acid addition salts are prepared by way of known process steps. Such a production method comprises the steps of providing a solution of the basic alkaloid, reacting, in a further step, said solution with equimolar amounts of a solution of the organic acid or - if the acid is liquid - reacting the solution directly with said acid, and isolating the addition salt thus obtained by means of common process steps.

In accordance with the invention, the above-described substances or compositions are employed in preparations for transdermal or transmucosal administration. They are used above all for pain control or in withdrawal therapies of drug addicts. Such preparations for transdermal or transmucosal administration are, for example, lotions, ointments, cremes, gels or sprays, transmucosal therapeutic systems, transdermal therapeutic systems (TTS) or iontophoretic devices. Such transdermal or transmucosal therapeutic systems are in principle known to those skilled in the art. They are described, for example, in "Therapeutische Systeme" [Klaus Heilmann, 4th ed., Ferdinand Enke Verlag, Stuttgart (1984)].

If the preparation for transdermal administration is a TTS, this comprises a - preferably active substance-imperm able

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- backing layer and a reservoir layer. The reservoir layer preferably contains 40 - 80%-wt polymer material. This polymer material is preferably selected from the group of polyacrylates, silicones or polystyrenes. Furthermore, the reservoir layer preferably contains 0.1 - 30%-wt plasticizer as well as the morphine alkaloid acid addition salts according to the invention in an amount of from 0.1 to 30%-wt.

The backing layer may consist of flexible or non-flexible material. Examples of materials used for its manufacture are polymer films or metal foils, such as aluminium foil, which are used on their own or coated with a polymer substrate. Textile fabrics may also be used, provided that the components of the reservoir can not penetrate the fabrics due to their physical properties.

In a preferred administration form the backing layer is a composite material of an aluminized layer.

The reservoir layer contains - as mentioned above - a polymer matrix and the active substance, the polymer matrix ensuring the coherence of the system. It comprises a base polymer and optionally further common additives. The selection of the base polymer is dependent on the chemical and physical properties of the salts according to the present invention. Examples of polymers are rubber, rubber-like synthetic homopolymers, copolymers or blockpolymers, polyacrylic acid esters and their copolymers, polyurethanes and silicones. In principle, any polymers are suitable which can also be used in the production of pressure-sensitive adhesives and which are physiologically acceptable. Especially preferred are those based on blockpolymers of styrene and 1,3-dienes, polyisobutylenes, silicones and acrylate-based and/or methacrylate-based polymers.

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What kind of common additives are employed depends on the polymer used: According to their function, they can be divided, for example, in tackifying agents, stabilizers, carriers and fillers. Physiologically acceptable substances suitable for this purpose are known to the man skilled in the art.

The reservoir layer has such self-adhesiveness as to ensure permanent contact to the skin. It may also have a multi-layered structure.

The selection of the plasticizer - which may simultaneously serve as a solvent - is dependent on the active substance in the polymer.

A removable protective layer, which is in contact with the reservoir layer and is removed prior to application, may also be made up of the same materials as are used for producing the backing layer, with the prerequisite that these materials have been rendered removable, such as, for example, by means of silicone treatment. Other removable layers are, for example, polytetrafluoroethylene, treated paper, cellophane, polyvinylchloride and the like.

A TTS will initially be present in an initial stage as a laminate. If the laminate is divided into formats suitable for therapy (patches) prior to application of the protective layer, the protective layer pieces to be applied subsequently may have a projecting end, with the aid of which said pieces can be removed more easily.

In the case of transmucosal administration of the salts according to the present invention, it is preferred to use a mucoadhesive additive for more rapid absorption through the mucous membrane.

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 Such additives are, for example, polyacrylic acid carboxymethylcellulose and other derivat d polysaccharides, especially acetyl starch or hydroxyethyl starch or combinations thereof.

The transdermal system may be prepared by homogeneously mixing the active substance together with the other components of the pressure-sensitive reservoir layers, optionally in solution, and applying same onto the - optionally active substance-impermeable - backing layer, whereupon the solvent(s) is/are removed. Subsequently, the adhesive layer is provided with a corresponding protective layer.

The invention will be illustrated in more detail by means of the following Figures and Examples:

The Figures show:

- Fig. 1: the  $^1\text{H}$ -NMR spectrum of the morphine base in  $\text{CDCl}_3$  at 400 MHz.  
 Fig. 2: the  $^1\text{H}$ -NMR spectrum of the morphine trimethylbenzoate in  $\text{CDCl}_3$  at 400 MHz.  
 Fig. 3: The table shows the association of the individual proton signals in the  $^1\text{H}$ -NMR spectrum of the morphine base as well as of the morphine trimethylbenzoate, according to their chemical shift (characterization as morphine salt).

By means of NMR spectroscopy it is possible to monitor the protonation of the alkaloid function in the morphine molecule. The salt formation has an impact on the electron distribution in the piperidine portion. A lower field shift of the proton resonance signals in the region of the base function shows that th protons there are de-

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shielded through salt formation. On the one hand, this is due to the acidic trimethylbenzoic acid proton being bonded by the free electron pair at the basic nitrogen, and, on the other hand, to the influence of the trimethylbenzoic acid residue.

Fig. 4: The Table shows the results of measurements of the penetration behaviour of various morphine salts according to the present invention, and of comparison substances. The preparations are self-prepared; identification was performed by means of IR-ATR and H-NMR spectrums.

Fig. 5: This diagram shows the permeation behaviour of morphine monomethyl sebacate in comparison to morphine base, in each case from one TTS, as described in Utilization Example 1. The penetration rate of the salt lies above that of the base by a factor of ca. 1.8. The incorporated amount of salt corresponds to 10%-wt morphine base, thus being equimolar to the reference TTS of the morphine base.

#### PRODUCTION EXAMPLE 1:

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1 g (3.5 mMol) water-free morphine base were dissolved, while heating, in 100 ml methanol. Once the base had been completely dissolved in methanol, a solution of 756 mg (3.5 mMol) monomethylsebacic acid in 20 ml methanol was added. The combined solutions were narrowed down in the rotary evaporizer. After ca. 48 h at 5 °C the morphine monomethyl sebacate had crystallized. Solvent residues were removed using a vacuum pump. The crystals had a melting point of 146 °C.

PRODUCTION EXAMPLE 2:

Production Example 1 was repeated, except that instead of the monomethylsebacic acid an equimolar amount of p-hydroxybenzoic acid was used.

PRODUCTION EXAMPLE 3:

Production Example 1 was repeated, with the exception that instead of monomethylsebacic acid an equimolar amount of oxoproline was used.

PRODUCTION EXAMPLE 4:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of hexanesulfonic acid was used.

PRODUCTION EXAMPLE 5:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of nicotinic acid was used.

PRODUCTION EXAMPLE 6:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of p-amino-benzoic acid was used.

PRODUCTION EXAMPLE 7:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of 2,4,6-trimethylbenzoic acid was used.

PRODUCTION EXAMPLE 8:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of lipoic acid was used.



PRODUCTION EXAMPLE 9:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of acetylglycin was used.

PRODUCTION EXAMPLE 10:

Production Example 1 was repeated, except that instead of the monomethylsebacic acid an equimolar amount of hippuric acid was used.

COMPARISON EXAMPLE 1:

Production Example 1 was repeated, with the exception that instead of the salt of monomethylsebacic acid and morphine, only an equivalent amount of morphine base was used.

COMPARISON EXAMPLE 2:

Production Example 1 was repeated, except that instead of monomethylsebacic acid an equimolar amount of propionic acid was used.

COMPARISON EXAMPLE 3:

Production Example 1 was repeated, with the exception that instead of monomethylsebacic acid an equimolar amount of formic acid was used.

UTILIZATION EXAMPLE 1:

1.654 g morphine monomethylsebacate (corresponding to 10%-wt morphine base) were incorporated in 2.346 g oleic acid. Subsequently, this was stirred until complete dissolution of the solid substance (ca. 15 minutes, visual control). The solution was then, again under stirring, stirred in portions into 12.3 g of a self-crosslinking acrylate polymer of 2-ethylhexyl acrylate, vinyl acetate and acrylic acid (48,8%-wt., in a solvent mixture ethyl acetate : heptane).

tane : ethanol : 2-propanol 39 : 13 : 22 : 26). This was then stirred for ca. 2 hours, at room temperature. The evaporation loss was compensated with ethyl acetate. 10 g 48.8%-wt. active substance-containing adhesive solution were yielded and coated onto an aluminized and siliconized polyethylene film. After removal of the solvents by drying for 30 minutes at up to 50 °C, the adhesive film was covered with a 15-µm-thick polyester film. Using appropriate cutting tools, the intended application surfaces were punched out and the margins removed through separation by lattice.

#### UTILIZATION EXAMPLE 2:

30 mg of morphine-p-hydroxybenzoate were suspended in 1.47 g olive oil. The 2%-wt trituration thus obtained was applied, using an application device, to excised nude guinea pig skin which, in turn, had been clamped into a FRANZ' diffusion cell tempered at 37 °C. As acceptor solution, 0.9% sodium chloride solution was used, which, under continued stirring, was likewise maintained at 37 °C and completely replaced by a new acceptor solution. The results of the amounts penetrated from the donor portion, determined through HPLC, are set out in Fig. 4.

#### UTILIZATION EXAMPLES 3 to 14:

Utilization Example 2 was repeated with the modification that instead of morphine-p-hydroxybenzoate, in the trituration the morphine salts of the Production Examples 3 to 10, or the substances of the Comparison Examples 1 to 3 were used. The results are likewise set out in Fig. 4.

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